# Research Roundup

A boisterous histone

A variant histone called H2A.Z (Htz1 in budding yeast) is an antisilencing protein, according to Marc Menenghini, Michelle Wu, and Hiten Madhani (University of California, San Francisco, CA). They propose that Htz1 protects the transcriptionally active euchromatic state from the threat of spreading heterochromatin.

When H2A.Z is added in vitro to replace H2A, the resulting nucleosomes are resistant to higher order condensation. But the in vivo significance of this result was unclear. Now, along comes the new array data. "We got this bizarre result," says Madhani. "The genes that were repressed [after Htz1 loss] were clustered near telomeres." Other repressed genes were huddled near the mating region, which is the other major silenced region in yeast chromatin.

The repression was partially reversed by deleting either the silencing protein Sir2 or a mating region silencing element. Repression after Htz1 deletion was associated with the spread
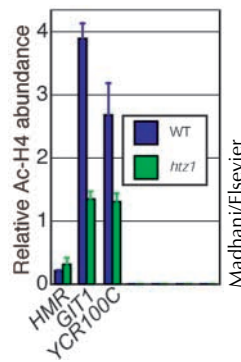
Htz1 protects euchromatic marks from encroaching heterochromatin.

Madhani/Elsevier

of Sir2 and Sir3 from both telomeres and the mating region into normally active, euchromatic regions, and reduced levels of euchromatin-associated marks such as acetylated histone H4.

A simple spreading event may not explain all, however. Only 30% of genes near telomeres require Htz1 to maintain their expression levels. And although Sir2 and acetylated H4 levels changed in euchromatic regions when Htz1 was deleted, they never reached the levels seen in heterochromatin.

Loss of a chromatin boundary element showed synergistic effects with Htz1 deletion, and Madhani believes there may be still other systems that protect against the insidious spread of heterochromatin. When those systems are understood, he says, we may realize that euchromatin has its own maintenance and spreading mechanisms and thus is "morally equivalent to heterochromatin." ∎

Reference: Meneghini, M.D., et al. 2003. *Cell.* 112:725–736.

How old mothers can have young offspring

All organisms, even as they themselves age, must give rise to progeny that are young not only chronologically but also biochemically. Now, Hugo Aguilaniu, Thomas Nyström (Göteborg University, Göteborg, Sweden), and colleagues show that budding yeast solves this problem by filtering oxidatively damaged proteins.

The group set out to see if protein carbonylation, an irreversible form of oxidative damage, increased with age in budding yeast. It did, which immediately led to another question. "How," asks Nyström, "do the daughters come out fresh"?

Nyström/AAAS
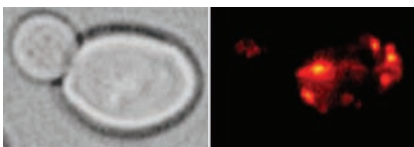
Carbonylated proteins (red) stay in the mother cell.

The daughters do, indeed, emerge with 3.6-fold less damage than their parents, and if the oxidative load is first boosted in the mother the ratio ratchets up to sixfold. This uneven segregation is dependent on the presence of Sir2p. This protein is required to prevent premature yeast aging, and was thought to operate in yeast solely by reducing the accumulation of toxic circles of rDNA.

The mechanism of oxidative filtering remains unclear. It is dependent on actin, which suggests two possible scenarios. The actin may block nearly all mother proteins from entering the bud, so that the bud is built almost entirely from new protein synthesis. Or carbonylated proteins may be selectively retained in the mother by proteins that use actin as a scaffold. Nyström is testing these possibilities and investigating whether mammalian stem cells might selectively off-load oxidized proteins into their differentiated progeny. ∎

Reference: Aguilaniu, H., et al. 2003. *Science.* 10.1126/science.1080418.
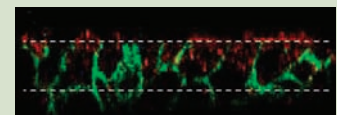
Hide and seek

A growth factor hides from its receptor in a different membrane domain, as demonstrated by Paola Vermeer, Michael Welsh (University of Iowa, Iowa City, IA), and colleagues. The separation normally prevents receptor activation, but can be overcome rapidly when activation is necessary.

The sneaky receptor is erbB2, whose activation by the ligand heregulin stimulates cellular migration and proliferation. Although both erbB2 and heregulin are expressed in airway epithelial cells, the slow division rate of these cells suggests that erbB receptors are not signaling. The Iowa group now shows that erbB2 is inactive because it is separated from its ligand by tight junctions. Whereas heregulin was found in the apical membrane of the epithelial cells, erbB2 resided on the basolateral surface.

Welsh/Macmillan

Separation of erbB2 (red) from its ligand, heregulin (green), limits receptor signaling in airway cells.

The spatial barrier offers a quick fix for damaged epithelia. "The instant any insult occurs," says Vermeer, "the system is already set up to repair damage without relying on transcription or translation." As predicted, a wound stimulus activated erbB2 rapidly (within one minute following injury). Blocking either erbB2 or heregulin delayed subsequent wound repair.

On the down side, pathological loss of the physical separation may cause problems in diseases such as asthma, in which tight junctions are not so tight. "When you have loose junctions, you may be chronically stimulating receptors," says Vermeer. Indeed, asthma patients often have thickened epithelial tissue. The group is now testing whether erbB2 activation accounts for this remodeling. ∎

Reference: Vermeer, P., et al. 2003. *Nature.* 422:322–326.

TEXT BY WILLIAM A. WELLS
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The Journal of Cell Biology

Making stripes

Somites, the precursors of vertebrae, striated muscle, and dermis, are laid down in a timed sequence from anterior to posterior. Now, Alexander Aulehla, Bernhard Herrmann (Max-Planck-Institut für Immunbiologie, Freiburg, Germany), and colleagues report that a gradient and two dueling molecular clocks, all driven directly or indirectly by Wnt3a, combine to create the striped pattern of somites.

The gradient and clock ideas have been proposed before. But, says Herrmann, "what was completely unclear was how the gradient and clock are coupled." That link is now provided by a single
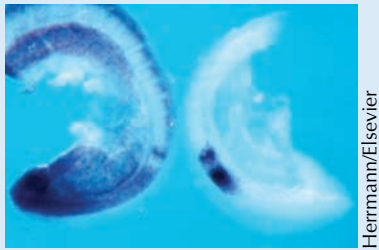
Axin2 (left) and the Notch pathway (right) oscillate out of phase to create somites.

protein, Wnt3a, which is connected to both processes.

Wnt3a came into the picture when the group discovered Wnt-dependent Axin2 expression in the tail bud and presomitic mesoderm (PSM). Axin2 expression was cyclic, but oscillated out of phase with the known oscillation of Notch pathway activity, which is also dependent on Wnt3a activity.

Known signaling pathways provide some plausible circuitry. Axin2 produced by Wnt pathway activity should both turn off the Wnt pathway (via a negative feedback loop) and turn on the Notch pathway (by binding to a negative regulator). The instability of Axin2 would later reverse the situation, leading to a continuous cycle.

The gradient idea arose because Wnt3a is made in the tail bud but can direct Axin2 expression throughout the PSM. High concentrations of Wnt3a near the tail bud prevent differentiation. But as the lengthening embryo puts more distance between the tail bud and the anterior, the level of Wnt3a in the anterior

PSM drops. Below a certain threshold of Wnt3a, the Notch pathway can take over and direct somite development.

If this gradient was acting alone, the end result would be a steadily moving front of differentiation. But, as Herrmann points out, "the boundary position has to move back in a periodic manner. For that purpose you need the clock."

The clock operates only above the threshold level of Wnt3a—below this the cells get stuck in the "Notch on (Wnt off)" state. Above the threshold, all cells cycle together. But each time a new "Wnt on" cycle starts, the cells just below the threshold will not be able to join their more posterior neighbors, and for the first time there will be a boundary between "Wnt on" and "Notch (stuck) on." This boundary is the key: it defines the division between somites. The boundary only arises when the more posterior, above threshold, region cycles back up into a "Wnt on" state, so it is only laid down periodically. ∎

Reference: Aulehla, A., et al. 2003. *Dev. Cell.* 4:395–406.

Chromosomes in the 'hood

It is almost unbearable (at least for scientists) to contemplate a complete lack of order. So, it comes as some relief that chromosomes may be positioned nonrandomly in the nucleus, thus giving rise to more frequent translocations between certain chromosomes.

The seeming chaos of mitosis led most researchers to believe that any such order would have to be reestablished after each division. But now Daniel Gerlich, Roland Eils (German Cancer Research Center, Heidelberg, Germany), Jan Ellenberg (EMBL, Heidelberg, Germany), and colleagues have found that positioning is maintained through mitosis by a timing mechanism.

Congressing chromosomes make a beeline for the metaphase plate, the group found, and thus preserve information about their relative position perpendicular to the spindle axis. But congression erases information about how far the chromosomes had to travel to reach the metaphase plate. Despite this, the group found that marked territories, chromosomes or centromeres reestablished their previous geographies after mitosis. (Conflicting conclusions were recently drawn by Walter et al. in these pages.)

Chromosomes reestablished their positions by initiating anaphase separation at different times. Chromosomes that

Marked chromosome areas are conserved through mitosis.

started anaphase later ended up on the side of the nucleus closest to the daughter cell. This ordering was jumbled by a heterochromatin-binding drug, so Eils suggests that chromosomes with larger regions of pericentric heterochromatin may stick to each other for longer and thus initiate anaphase later. Such a mechanism should work through multiple cell divisions.

It is unlikely that the chromosomes are placed in locations with very different biochemistry: the placement is too rough, and most relevant proteins are in any case very mobile. So maybe the locations are merely a passive readout of kinetochore structure. Eils doesn't buy this argument. "I think Nature has invented this for a particular reason," he says, "but I don't yet know what reason." ∎

References: Gerlich, D., et al. 2003. *Cell.* 10.1016/S0092867403001892. Walter, J., et al. 2003. *J. Cell Biol.* 160:685–697.